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ORIGINAL ARTICLE

Adverse events reported for Mirena levonorgestrel-releasing intrauterine device in France and impact of media coverage

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Aims: In 2017, concerns regarding adverse events (AEs) associated with the Mirena levonorgestrel intrauterine device were largely echoed in the media in France. This resulted in a tremendous reporting of AEs to pharmacovigilance centres. The aim of this study was to describe the reporting of AEs regarding Mirena in France and to study the impact of media coverage on this reporting.

Methods: All cases reports involving Mirena recorded in the French national pharmacovigilance database from marketing (21 July 1995) until 04 August 2017 were extracted. To allow studying the influence of mediatisation, reports were described separately for the periods preceding and following the observed media coverage peak (15 May 2017).

Results: Overall, 3224 reports were considered, 510 (15.8%) recorded before the media coverage peak, and 2714 (84.2%) after. Before the peak, 76.5% of reports originated from health professionals; median time-to-report was of 5.5 months (interquartile range: 1.7–18.6), and median number of AEs per report was 1 (range: 1–17). After the peak, 98.6% originated from patients; median time-to-report was 21 months (interquartile range: 8.1–45.5), and median number of AEs per report was 6 (range: 1–37). After the peak, most reports mentioned anxio-depressive disorders (38.8 *vs* 10.6% before) or sexual disorders (47.3 *vs* 6.9%). Other emphasised AEs were weight increase (42.3 *vs* 10.2%) and pain (gastrointestinal, 19.1 *vs* 3.5%; musculoskeletal, 22.2 *vs* 4.5%).

Conclusion: This study highlighted the importance of mediatisation impact on spontaneous reporting with changes concerning amounts of reports, type of reporter, and type of reported AEs. For Mirena, this led to generate signals regarding anxio-depressive and sexual disorders.

KEYWORDS

drug safety, gynaecology/obstetrics, pharmacovigilance

The authors confirm that the PI for this paper is Antoine Pariente. This study was a database-based study; therefore, there was no direct clinical responsibility for patients.

1 | INTRODUCTION

A **levonorgestrel**-releasing intrauterine device (IUD) is a long-acting reversible method of contraception. Since 1990, the Mirena IUD has been available in Europe; Mirena releases locally 20 μg/day of levonorgestrel, a second-generation progestin that thickens cervical mucus and inhibits sperm motility and capacitation. Its atrophic effect on endometrium has also led to its use in endometriosis, endometrial hyperplasia or menorrhagia.[1] In France, IUDs (levonorgestrel-releasing or copper) are the second most used method for contraception and are used by around 1/4 of women using a contraceptive method.[2,3] IUD is considered as one of the most effective and convenient reversible methods of contraception currently available, with lower rate of adverse events (AEs) in comparison to oral contraceptives.[4-6] As for all IUDs, the use of levonorgestrel-releasing IUD carries several risks including a risk of ectopic pregnancy, pelvic pain and device expulsion.[1,6,7] Other AEs have been described, in particular hormonal-related AEs, as weight gain, libido loss, abnormal bleeding (e.g. spotting, amenorrhoea) and depression.[1,8,9] Nevertheless, studies have been performed that highlight a high satisfaction rate in women using levonorgestrel-releasing IUD.[1]

In 2017, concerns regarding AEs associated with the use of levonorgestrel-releasing IUD (mainly Mirena) emerged in Germany before spreading into France, first in social networks, then in traditional media.[10] In Germany, some patients launched Facebook groups and completed a petition in February 2017, requesting the inclusion of AEs (mainly psychiatric: anxiety, panic attacks, mood changes, sleep disorders and restlessness) in the Summary of Product Characteristics (SPC) of all levonorgestrel IUDs. Recriminations also related to the perceived limited information given at the moment the device was proposed and to the difficulty of accessing the information afterwards. After an analysis of the German pharmacovigilance national database, the Pharmacovigilance Risk Assessment Committee requested an evaluation of the signals raised.[10] As a consequence, similar Facebook groups were constituted in France, and numerous discussions arose in patients' online fora. After these gained sufficient volume, the women's press put an emphasis on different potential levonorgestrel-releasing IUD related AEs including depression, irritability, asthenia, hair loss, dysmenorrhoea, headache, abdominal pain and loss of libido, in addition to those identified in Germany. While insisting on these potential safety issues and on the importance of reporting, electronic patient communities also widely invoked the lack of initial information about potential AEs of the device and the difficulty of compensating it by reading the SPC, often thrown away with the box at the time of the insertion.[11] The media coverage peak occurred in May 2017 with an apex around 15 May, which resulted in a tremendous wave of reporting of AEs from patients to French pharmacovigilance centres. Noticeably, this reporting mainly used the newly launched governmental web-portal for the reporting of AEs whatever the cause, which allows each and any to report straight to the French pharmacovigilance national system (https://signalement.social-sante.gouv.fr; date of launch: 13 March 2017).[12] This situation led the French Agency for Medicines and Health Products Safety (*Agence Nationale de Sécurité des Médicaments et des produits de santé* [ANSM]) to request the conduct of a pharmacovigilance national-level study to review the safety profile of levonorgestrel-releasing IUDs marketed in France—Mirena and Jaydess.

The aim of this study was to evaluate the reporting of AEs for Mirena to the French Network of Pharmacovigilance Centres and to evaluate the influence of media coverage on this reporting. Due to the low number of reports concerning Jaydess, this study focused on Mirena.

What is already known about this subject

- Intrauterine devices (IUD) are used by around 1/4 of women using a contraceptive method.
- IUD are considered to have a lower rate of adverse events in comparison to oral contraceptives.
- The mediatisation in May 2017 resulted in a tremendous wave of reporting of adverse events from patients.

What this study adds

- Reported adverse events involving the Mirena IUD changed drastically after media coverage and reporting modifications concerned adverse events type, seriousness, amount, and reporter.
- After mediatisation, events were mostly patient-reported and essentially concerned anxio-depressive or sexual disorders.
- This questioned the real frequency of these adverse events and advocated for their search in Mirena users.

2 | METHODS

2.1 | Data source

Data were extracted from the French national pharmacovigilance database (*Base Nationale de Pharmacovigilance*).[13,14] This database includes all adverse drug reactions spontaneously reported to the French Regional Pharmacovigilance Centres since 1985, representing nearly 600 000 case reports. It is managed by the ANSM and supplied with data by all French Regional Pharmacovigilance Centres.[13] Adverse drug reaction spontaneously reported directly to the marketing authorisation holders were not available in this database. All reports are pharmacologically and medically reviewed by the French Regional Pharmacovigilance Centre teams before they are entered in the database. Each case report can include one or several AEs; all AEs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.[15]

2.2 | Data extraction and selection

ANSM provided all case reports involving Mirena recorded in the *Base Nationale de Pharmacovigilance* from marketing until 4 August 2017 and in which Mirena was considered as *suspect* or as an interacting drug according to the accountability World Health Organisation criteria. Data available from case reports included: (i) patient data: sex, age; (ii) characteristics of the reported AEs: description of the AEs coded according to the MedDRA classification, seriousness; (iii) drugs involved (Mirena and others): name, role in the AE (suspect, interacting, concomitant). AEs were defined as serious if they resulted in death, life-threatening condition, hospitalisation or prolongation of hospitalisation, persistent or significant disability/incapacity, congenital anomalies or birth defects, or were judged as other serious medical situation (i.e. resulting in specific medical care or considered to have significantly altered patients quality of life).[16]

2.3 | Statistical analysis

A descriptive analysis of the reported cases was performed. Number and proportion were used for qualitative variables, and median and interquartile range (IQR) for continuous variables. Reports were described in terms of type of reporter (health professional *vs* consumer), time-to-report (delay from date of onset to date of reporting), number of AEs per report, age and sex of the patient, and seriousness. AEs were classified according to MedDRA system organ class, high level term and preferred term (PT). The descriptions were stratified according to the media coverage peak, occurred on 15 May 2017. The first period elapsed from marketing until 14 May 2017; the second ranged from 15 May 2017 until the date data were extracted from the database (i.e. 4 August 2017). All these analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA).

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPSGuide to PHARMACOLOGY.[17]

3 | RESULTS

3.1 | Population characteristics and overall description of case report

Among the 3224 case reports identified for Mirena, 510 (15.8%) were recorded before the media coverage peak and 2714 (84.2%) after this. Most of reported cases were serious: 272 (53.3%) before the media coverage peak and 1789 (65.9%) after the media coverage peak. Median age of patients was similar in the 2 studied periods (37 years, IQR: 32–42 *vs* 36 years, 31–41).

3.2 | Quantitative description of reporting for Mirena, before and after the media peak

Before the media coverage peak, 76.5% of case reports (390/510) were notified by health professionals. This changed drastically after the media peak where 98.6% (2675/2714) of the case reports originated from patients.

Before the peak, serious cases mostly corresponded to AEs that had led to hospitalisation or prolongation of existing hospitalisation (55.2%) whereas, after the peak, they mostly corresponded to AEs considered as clinically relevant by the reporter (93.3%; Table 1).

Within the case reports, the number of AEs (expressed in PT) and the number of system organ classes considerably increased between the 2 periods. Before the media coverage peak, a median of 1 PT

TABLE 1 Characteristics of included case reports before and after the media coverage peak (n = 3224)

Characteristics, n (%)	Before the media coverage peak, n = 510	After the media coverage peak, n = 2714
Median age, years [IQR]	37 [32–42]	36 [31–41]
Missing data	32 (6.3)	215 (7.9)
Sex		
Male	2 (0.4)	0 (0.0)
Female	508 (99.6)	2711 (99.9)
Missing data	0 (0.0)	3 (0.1)
Reporter qualification		
Health professional[a]	390 (76.5)	38 (1.4)
Consumer	119 (23.3)	2675 (98.6)
Missing data	1 (0.2)	1 (0.0)
Seriousness		
Yes	272 (53.3)	1789 (65.9)
No	238 (46.7)	925 (34.1)
Seriousness criteria[b]		
Death	3 (1.1)	0 (0.0)
Life-threatening	15 (5.5)	4 (0.2)
Caused/prolonged hospitalisation	150 (55.2)	106 (5.9)
Incapacity	7 (2.6)	26 (1.5)
Other serious medical situation	101 (37.3)	1665 (93.3)
Number of adverse events		
Preferred terms, median [range]	1 [1–17]	6 [1–37]
System organ class, median [range]	1 [1–12]	5 [1–17]
Median time-to-report, months [IQR]	5.5 [1.7–18.6]	21.0 [8.1–45.5]
Missing data	87 (17.1)	1203 (44.3)

[a]Corresponding to physician, pharmacist and other health professional;

[b]Patients can have >1 seriousness criterion.

IQR: interquartile range

was coded by case report (range: 1–17). It increased to 6 (range: 1–37) after the media coverage peak (Table 1).

Regarding the time-to-report, the median time from the onset of AE to the reporting was 5.5 months (IQR: 1.7 *vs* 18.6) before and 21.0 months (IQR: 8.1 *vs* 45.5) after the media coverage peak (Table 1).

The launch of government web-portal did not result in increased reporting, yet the apex of the media coverage corresponded to the apex of declarations, proportionally to the total declarations (Figure 1).

3.3 | Qualitative description of reporting for Mirena, before and after the media coverage peak

Before the media coverage peak, the most frequently reported AEs were skin and subcutaneous tissue disorders (29.4%), and especially corresponded to events of acnes (10.4%) and alopecia (9.0%). Other main reported events were psychiatric disorders (20.7%; including depressive disorders [10.6%] and sexual desire troubles [6.9%; mainly relating to libido decrease]), nervous system disorders (20.7%; including headaches [6.9%] and central nervous system haemorrhages and cerebrovascular accidents [3.5%]), general disorders and administration site conditions (19.2%), and reproductive system and breast disorders (12.5%; including breast pain [3.3%] and vaginal discharge [0.6%]); AEs related to genital bleedings were heterogeneous: 1.8% concerned episodes of decreased menstruation and 2.9% concerned increased menstruation. Within the other reported AEs, those related to pregnancy, puerperium and perinatal conditions represented 11.5% of all case reports and 17.6% of serious case reports; they included in particular ectopic pregnancy (4.3% of all reported AEs; Table 2).

After the media coverage peak, most reports mentioned AEs related to sexual desire disorders (47.3%), depressive disorders (38.8%), anxiety (32.1%), and emotional and mood disorders (25.5%). The modification in reporting was also accompanied by the emerging of reports for new types of AEs, in particular gastrointestinal and abdominal pain (19.1%); musculoskeletal and connective tissue pain and discomfort (22.2%); inner ear signs and symptoms (22.6%); physical examination procedures and organ system status, mainly corresponding to weight increase (42.3%); and asthenic conditions (48.0%; Table 2).

The other frequently reported events appeared similar to those reported before the peak, yet in larger proportions. They involved skin and subcutaneous tissue disorders (51.1%; including acne [13.9%], alopecia [28.5%] and hypertrichosis [13.9%]) and nervous system disorders (53.9%; including headaches [20.3%], memory loss [11.3%] and 5 [0.2%] central nervous system haemorrhages and cerebrovascular accidents).

Finally, pregnancy, puerperium and perinatal conditions accounted for a limited proportion of the reports (1.4%; Table 2).

4 | DISCUSSION

The present work provides a new illustration of the effect of media attention on spontaneous reporting with changes concerning the number of reports, the type of the reporter and the type of the reported events. The phenomenon was herein amplified by the echo found in social networks and the recent launch of a governmental web-reporting tool designed for both health professionals and patients. Altogether, this led to a tremendous increase in the number of reports (from 510 reports over 25 years to <2700 reports in 3 months), nature of reports (1–6 AEs per report), and reports origin with a rise of the proportion of patient reports from 23.3 to 98.6%.

If the governmental web-reporting tool clearly facilitated patients reporting concerning Mirena, no significant increase in the number of reports was observed for other drugs over the period.[18] However,

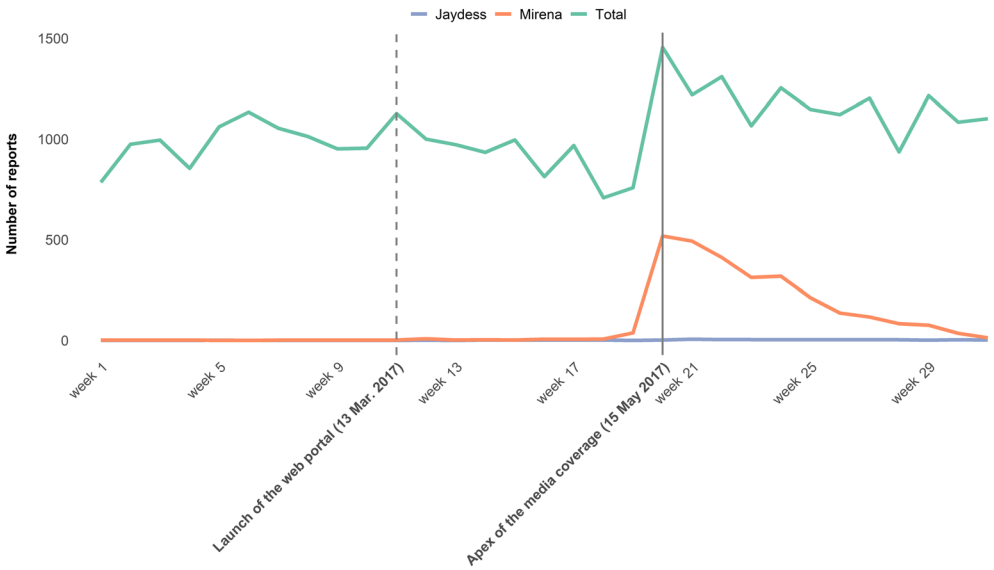

FIGURE 1 Reports to French network of pharmacovigilance Centres from 1 January 2017 to 4 August 2017.

TABLE 2 Description of serious adverse drug reactions before and after the media coverage peak (n = 3224)

	Before the media coverage peak, n = 510		After the media coverage peak, n = 2714	
Characteristics, n (%)	**Not serious n = 238**	**Serious n = 272**	**Not serious n = 925**	**Serious n = 1789**
Cardiac disorders	6 (2.5)	8 (2.9)	101 (10.9)	245 (13.7)
Rate and rhythm disorders NEC	4 (1.7)	6 (2.2)	76 (8.2)	151 (8.4)
Cardiac signs and symptoms NEC	1 (0.4)	1 (0.4)	24 (2.6)	86 (4.8)
Ear and labyrinth disorders	9 (3.8)	7 (2.6)	200 (21.6)	425 (23.8)
Inner ear signs and symptoms	9 (3.8)	7 (2.6)	198 (21.4)	417 (23.3)
Skin and subcutaneous tissues disorders	105 (44.1)	45 (16.5)	487 (52.6)	900 (50.3)
Acne	42 (17.6)	11 (4.0)	126 (13.6)	251 (14.0)
Alopecia	35 (14.7)	11 (4.0)	279 (30.2)	495 (27.7)
Hypertrichosis	15 (6.3)	3 (1.1)	138 (14.9)	239 (13.4)
Pruritus NEC	7 (2.9)	2 (0.7)	21 (2.3)	45 (2.5)
Urticaria	8 (3.4)	6 (2.2)	8 (0.9)	18 (1.0)
Reproductive system and breast disorders	42 (17.6)	22 (8.1)	404 (43.7)	794 (44.4)
Ovarian and fallopian tube cysts and neoplasms	5 (2.1)	4 (1.5)	53 (5.7)	158 (8.8)
Menstruation and uterine bleeding NEC	5 (2.1)	1 (0.4)	40 (4.3)	71 (4.0)
Menstruation with decreased bleeding	4 (1.7)	1 (0.4)	20 (2.2)	32 (1.8)
Menstruation with increased bleeding	4 (1.7)	2 (0.7)	28 (3.0)	51 (2.9)
Reproductive tract signs and symptoms NEC	4 (1.7)	6 (2.2)	45 (4.9)	100 (5.6)
Breast signs and symptoms	15 (6.3)	4 (1.5)	185 (20.0)	331 (18.5)
Vulvovaginal signs and symptoms	5 (2.1)	2 (0.7)	79 (8.5)	165 (9.2)
Nervous system disorders	49 (20.6)	57 (21.0)	507 (54.8)	957 (53.5)
Headaches NEC	20 (8.4)	15 (5.5)	198 (21.4)	354 (19.8)
Migraine headaches	19 (8.0)	7 (2.6)	201 (21.7)	404 (22.6)
Central nervous system haemorrhage and cerebrovascular accident	0 (0.0)	18 (6.6)	1 (0.1)	4 (0.2)
Paresthesia and dysesthesia	5 (2.1)	3 (1.1)	90 (9.7)	191 (10.7)
Memory loss (excluding dementia)	2 (0.8)	6 (2.2)	91 (9.8)	215 (12.0)
Neurological signs and symptoms NEC	3 (1.3)	3 (1.1)	19 (2.1)	49 (2.7)
Gastrointestinal disorders	30 (12.6)	16 (5.9)	335 (36.2)	648 (36.2)
Gastrointestinal and abdominal pain	9 (3.8)	9 (3.3)	196 (21.2)	323 (18.1)
Flatulence, bloating and distension	8 (3.4)	2 (0.7)	112 (12.1)	221 (12.4)
Nausea and vomiting symptoms	8 (3.4)	2 (0.7)	65 (7.0)	150 (8.4)
Pregnancy, puerperium and perinatal conditions	11 (4.6)	48 (17.6)	9 (1.0)	28 (1.6)
Spontaneous abortion	0 (0.0)	5 (1.8)	0 (0.0)	4 (0.2)
Maternal complications of pregnancy NEC	0 (0.0)	22 (8.1)	0 (0.0)	13 (0.7)
Unintended pregnancy	3 (1.3)	11 (4.0)	0 (0.0)	1 (0.1)
Musculoskeletal and connective tissue disorders	29 (12.2)	17 (6.3)	312 (33.7)	686 (38.3)
Muscle pain	6 (2.5)	4 (1.5)	58 (6.3)	128 (7.2)
Musculoskeletal and connective tissue pain and discomfort	17 (7.1)	6 (2.2)	193 (20.9)	410 (22.9)
Joint-related signs and symptoms	6 (2.5)	8 (2.9)	98 (10.6)	189 (10.6)
Eye disorders	9 (3.8)	9 (3.3)	134 (14.5)	254 (14.2)
Partial vision loss	0 (0.0)	1 (0.4)	16 (1.7)	39 (2.2)
Visual disorders NEC	5 (2.1)	5 (1.8)	97 (10.5)	180 (10.1)

(Continues)

TABLE 2 (Continued)

Characteristics, *n* (%)	Before the media coverage peak, *n* = 510		After the media coverage peak, *n* = 2714	
	Not serious *n* = 238	Serious *n* = 272	Not serious *n* = 925	Serious *n* = 1789
Psychiatric disorders	54 (22.7)	52 (19.1)	745 (80.5)	1569 (87.7)
Emotional and mood disturbance NEC	16 (6.7)	10 (3.7)	226 (24.4)	466 (26.0)
Anxiety symptoms	15 (6.3)	17 (6.3)	247 (26.7)	623 (34.8)
Depressive disorders	22 (9.2)	32 (11.8)	273 (29.5)	779 (43.5)
Sexual desire disorders	20 (8.4)	15 (5.5)	419 (45.3)	866 (48.4)
Investigations	38 (16.0)	24 (8.8)	378 (40.9)	782 (43.7)
Physical examination procedures and organ system status	34 (14.3)	20 (7.4)	373 (40.3)	774 (43.3)
Liver function analysis	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (0.4)	48 (17.6)	3 (0.3)	25 (1.4)
Reproductive tract and breast procedural complications	0 (0.0)	46 (16.9)	0 (0.0)	10 (0.6)
General disorders and administration site conditions	45 (18.9)	55 (20.2)	489 (52.9)	967 (54.1)
Complications associated with device NEC	1 (0.4)	6 (2.2)	1 (0.1)	4 (0.2)
Pain and discomfort NEC	2 (0.8)	4 (1.5)	36 (3.9)	124 (6.9)
Asthenic conditions	20 (8.4)	20 (7.4)	438 (47.4)	866 (48.4)
Oedema NEC	6 (2.5)	2 (0.7)	13 (1.4)	19 (1.1)
Therapeutic and nontherapeutic responses	8 (3.4)	19 (7.0)	0 (0.0)	0 (0.0)
General signs and symptoms NEC	9 (3.8)	5 (1.8)	25 (2.7)	34 (1.9)

NEC: not elsewhere classified

July and August 2017 also corresponded to the Levothyrox scandal in France, with a significant increase in reports (around 17 000 cases), via the government web-portal and also by mail (e-mail and post).[19] Furthermore, the nature of reported AEs differed importantly between the 2 periods, patient reports including in most cases the mention of either anxio-depressive or sexual disorders. The reporting performed by patients after the peak also largely involved AEs, which were previously little reported by health professionals such as pain (gastrointestinal or musculoskeletal), alopecia or headache. Almost all these events are described in the SPC. Moreover, the anxio-depressive safety signal was found in a population-based cohort study of the safety of the Mirena levonorgestrel IUD compared to copper IUDs and with another recent observational study.[20,21]

The media coverage peak highlighted and broadcasted information about AEs of Mirena, informing the users that their symptoms could be related to potential AEs of their levonorgestrel-releasing IUD they were unaware of. Indeed, many consumers reported long-standing symptoms, such as depression, weight gain, abdominal pain or breast tenderness, which they had not attributed previously to their levonorgestrel-releasing IUD. Among reported AEs, potential hormonal-related AEs as headache, dysmenorrhoea, depression, breast tenderness or weight gain were frequent. These AEs were consistent with those highlighted in the media, particularly dysmenorrhoea, headache, abdominal pain or mood disorders. These AEs have been described in randomised clinical trials comparing levonorgestrel-releasing IUD to copper IUD: patients with levonorgestrel-releasing IUD reported significantly more depression, acne, headache, weight change and breast tenderness in comparison to patients with copper IUD.[9,22] Conversely, device-related AEs as abdominal pain were not more frequent in levonorgestrel-releasing IUD users in comparison to copper IUD users.[9] Overall, most of the reported AEs were known since first clinical trials conducted at the end of 1980s. The media coverage peak thus resulted in a marked *notoriety bias*, defined as an alteration in the balance of reporting between reactions due to an alert and resulting in the spurious perception of a drug-AEs association.[23] The important increase in time-to-report, from 5.5 months before to 21.0 months after the media coverage confirmed the notoriety bias suggesting that the mediatisation led to reporting of events previously neglected (or at least not reported). It is also likely that the campaign for reporting supported on social network was accompanied by an information leading to a better knowledge of pre-existing reporting tools (patients could, before the web-portal, contact the Regional Pharmacovigilance Centres by phone, email, fax or post). Usually, the notoriety bias follows alerts from health agencies, with the objective of limiting the exposure of patients at risk of AEs and thus reducing the risk of a given AE occurring. In the present case, the alert was launched on social media and accompanied by several testimonies, leading to a wave of comments and mistrust towards the medical community. To encourage the medical community to take this alert into account, a wave of reporting was encouraged by patient groups.

Despite this, a major concern of consumers was the absence of information about AEs at the time of IUD insertion, particularly hormonal-related AEs.[11] This lack of information or at least, of efficient information, has been highlighted for other types of care.[24,25] In the situation herein investigated, it might have played an important role in the massive patient-reporting that followed the media coverage peak. More than 90% of reports were declared to involve *Other serious (medical important events)*, essentially owing to the reporter's appraisal of the AEs consequences on patients' family, work or social life. Impact of social media on reporting trends has been highlighted in several studies, relating in particular that AEs reported by patients provided more insight into impact of AEs in daily life.[26-28] However, few studies involved active patients' groups. The most important to date could potentially concern that raised for Levothyrox in France, which was accompanied by a reporting wave of such importance that it modified the results of World Health Organisation analytics.[19]

Several studies estimating the safety of levonorgestrel-releasing IUD concluded that patient education regarding potential AEs was essential.[1,8,29] This was illustrated for gynaecological bleedings, which constitute frequent concerns for women using levonorgestrel-releasing IUD, with either decreased bleeding, amenorrhoea or conversely increased bleeding being the first reason for discontinuing using such devices.[8] Regarding this, Backman *et al*. demonstrated that women who received information about the possibility of amenorrhoea were more satisfied than the less informed women.[29]

Aside from this and the lessons to be taken from this reporting event and its origins, this study allowed performing an update of Mirena safety assessment owing to pharmacovigilance data. The main signals arising from this were that of frequencies could potentially be much higher than expected for some known or suspected AEs of Mirena such as of anxio-depressive disorders, sexual disorders, alopecia or headache. Two main limitations need to be mentioned regarding the results for these events. First the corresponding reports mostly originated from patients and AEs were not medically confirmed; some of the cases can thus not fully correspond to the event reported. Overall patient reports presented with a higher amount of missing data for comorbidities, concomitant medications, and time to report. Only the latter was used in this study, with around 17% of missing data for healthcare professional reported events and around 44% for patient reported events. As these patient-reported cases concerned older AEs, it might be that the time to report estimated for patient cases was underestimated. Second, as pharmacovigilance data can only provide incidences of reporting and not incidences of occurrence for events, such signals should be investigated in complementary pharmacoepidemiology studies. Moreover, the analyses did not consider reports made to the marketing authorisation holders.

Further data are needed for other serious but much rarer events for which the medical investigation as informed in reports was often limited or mentioned the presence of other well-known risk factors. These included especially cerebrovascular accidents and vision loss, which had moreover not been specifically spotted in the media.

5 | CONCLUSION

The present study highlighted the importance of mediatisation impact on spontaneous reporting, especially when patient-reporting is facilitated by specifically designed tools. For the situation of the Mirena IUD, this led to generate signals regarding the magnitude of the frequency of anxio-depressive or sexual disorders for instance. As patients become progressively a primary source of reporting, valuable and complementary to that of professionals, these results are also a plea for the developing of an education programme on reporting, especially for the data necessary for the evaluation of a case, such as the onset date of the AE. Initiatives in this domain already exist for patients receiving specific care. We believe more global initiatives should be envisioned, that would be available to the general population.

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COMPETING INTERESTS

The study was conducted in the context of a national pharmacovigilance follow-up for which the Centre de Pharmacovigilance de Bordeaux was appointed by the ANSM. The ANSM had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and the decision to submit the manuscript for publication. This publication represents the views of the authors and does not necessarily represent the opinion of the ANSM.

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CONTRIBUTORS

C.L., Am.G., G.M-S. and A.P. conceived the study. C.L., A.G., Au.G., M-C.P–P, J.B., G.M-S. and A.P. were involved in data collection. C.L., Am.G., G.M-S. and A.P. analysed and interpreted the data. All authors contributed to the preparation of the manuscript and approved the final manuscript for submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the ANSM. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the ANSM.

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REFERENCES

1. Beatty MN, Blumenthal PD. The levonorgestrel-releasing intrauterine system: safety, efficacy, and patient acceptability. *Ther Clin Risk Manag*. 2009;5:561-574.
2. Santé publique France. [Les Françaises et la contraception: premières données du Baromètre santé 2016]. 2017. Available from: https://www.santepubliquefrance.fr/Actualites/Les-Francaises-et-la-contraception-premieres-donnees-du-Barometre-sante-2016. Accessed December 20, 2018.
3. [Méthode contraceptives: Focus sur les méthodes les plus efficaces disponibles]. Paris, France: Haute Autorité de Santé. Available from: https://www.has-sante.fr/portail/upload/docs/application/pdf/2013-03/synthese_methodes_contraceptives_format2clics.pdf. Accessed December 20, 2018.
4. Trussell J. Contraceptive failure in the United States. *Contraception*. 2011;83(5):397-404.
5. Winner B, Peipert JF, Zhao Q, et al. Effectiveness of long-acting reversible contraception. *N Engl J Med*. 2012;366(21):1998-2007.
6. Stoddard A, McNicholas C, Peipert JF. Efficacy and safety of long-acting reversible contraception. *Drugs*. 2011;71(8):969-980.
7. Nelson AL. LNG-IUS 12: a 19.5 levonorgestrel-releasing intrauterine system for prevention of pregnancy for up to five years. *Expert Opin Drug Deliv*. 2017;14(9):1131-1140.
8. Kailasam C, Cahill D. Review of the safety, efficacy and patient acceptability of the levonorgestrel-releasing intrauterine system. *Patient Prefer Adherence*. 2008;2:293-302.
9. Andersson K, Odlind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomized comparative trial. *Contraception*. 1994;49(1):56-72.
10. European Medicine Agency. Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 6–9 February 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2017/05/WC500226848.pdf. Accessed December 20, 2018.
11. ['Une bombe dans l'utérus': la mobilisation contre de nombreux effets secondaires du stérilet Mirena prend de l'ampleur]. LCI. Available from: https://www.lci.fr/sante/sterilet-mirena-une-bombe-dans-l-uterus-partie-de-facebook-la-mobilisation-contre-de-nombreux-effets-secondaires-prend-de-l-ampleur-2053822.html. Accessed December 20, 2018
12. [Portail de signalement des événements sanitaires indésirables]. Available from: https://signalement.social-sante.gouv.fr/psig_ihm_utilisateurs/index.html#/accueil. Accessed December 20, 2018.
13. Moore N, Biour M, Paux G, et al. Adverse drug reaction monitoring: doing it the French way. *Lancet Lond Engl*. 1985;2:1056-1058.
14. Moore N, Noblet C, Kreft-Jais C, Lagier G, Ollagnier M, Imbs JL. French pharmacovigilance database system: examples of utilisation. *Therapie*. 1995;50:557-562.
15. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf*. 1999;20(2):109-117.
16. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000;356(9237):1255-1259.
17. Harding SD, Sharman JL, Faccenda E, et al. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucl Acids Res*. 2018;46:D1091-D1106.
18. [Agence nationale de sécurité du médicament et des produits de santé. Rapport d'activité 2017].
19. Khouri C, Revol B, Lepelley M, Mallaret M, Cracowski J-L. Impact of the 'French Levothyrox crisis' on signal detection in the World Health Organization pharmacovigilance database. *Pharmacoepidemiol Drug Saf*. 2018;27(12):1427-1428.
20. Bosco-Lévy P, Gouverneur A, Langlade C, Miremont G, Pariente A. Safety of levonorgestrel 52mg intrauterine system compared to copper intrauterine device: a population-based cohort study. *Contraception* 2019;99(6):345-349.
21. Slattery J, Morales D, Pinheiro L, Kurz X. Cohort study of psychiatric adverse events following exposure to Levonorgestrel-containing intrauterine devices in UK general practice. *Drug Saf*. 2018;41(10):951-958.
22. Eisenberg DL, Schreiber CA, Turok DK, et al. Three-year efficacy and safety of a new 52-mg levonorgestrel-releasing intrauterine system. *Contraception*. 2015;92(1):10-16.
23. Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. *Drug Saf*. 2007;30(10):891-898.
24. European Medicines Agency - News and Events - European Medicines Agency to review third- and fourth-generation combined oral contraceptives. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/01/news_detail_001700.jsp&mid=WC0b01ac058004d5c1. Accessed December 20, 2018.
25. Angus-Leppan H, Liu RSN. Weighing the risks of valproate in women who could become pregnant. *BMJ*. 2018;361:k1596.
26. van Hunsel F, Passier A, van Grootheest K. Comparing patients' and healthcare professionals' ADR reports after media attention: the broadcast of a Dutch television programme about the benefits and risks of statins as an example. *Br J Clin Pharmacol*. 2009;67(5):558-564.
27. Inácio P, Cavaco A, Airaksinen M. The value of patient reporting to the pharmacovigilance system: a systematic review. *Br J Clin Pharmacol*. 2017;83(2):227-246.
28. Bonaldo G, Vaccheri A, D'Annibali O, Motola D. Safety profile of human papilloma virus vaccines: an analysis of the US vaccine adverse event reporting system from 2007 to 2017. *Br J Clin Pharmacol*. 2019;85(3):634-643.
29. Backman T, Huhtala S, Luoto R, Tuominen J, Rauramo I, Koskenvuo M. Advance information improves user satisfaction with the levonorgestrel intrauterine system. *Obstet Gynecol*. 2002;99(4):608-613.

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